

Description

[Pharmaceutical Composition for the Treatment of Itch]

BACKGROUND OF INVENTION

[0001] Itch is a well known sensory state associated with the desire to scratch. As with pain, itch can be produced by a variety of chemical, mechanical, thermal or electrical stimuli. In addition to the difference in the sensory quality of itch and pain, they also differ in that (1) itch, unlike pain, can only be evoked from the superficial layers of skin, mucosa, and conjunctiva, and (2) itch and pain usually do not occur simultaneously from the same skin region; in fact, mildly painful stimuli, such as scratching, are effective in eliminating itch. In addition, the application of histamine to skin produces itch but not pain. Itch and pain are further dissociated pharmacologically: itch appears to be insensitive to opiate and non-steroidal anti-inflammatory drug (NSAID) treatment, both of which are effective in treating pain.

[0002] Although itch and pain are of a class in that both are modalities of nociception transmitted by small unmyelinated C fibers, evidence that itch is not just a variety of low threshold pain is overwhelming. Itch leads to the reflex or urge to scratch; pain leads to withdrawal. Removal of the epidermis eliminates itch but causes pain. Analgesics, particularly opioids, relieve pain but often cause itch (see, for example J. Am. Acad. Derm. 24: 309–310, 1991). There can be no doubt that itching is of eminent clinical importance; many systemic and skin diseases are accompanied by persistent or recurrent itch attacks. Current knowledge suggests that itch has several features in common with pain but exhibits intriguing differences as well (see, for example, W. Mager, IASP Newsletter, pp. 4–7, September/October 1996).

[0003] Experimental focal itch stimuli are surrounded by a halo of seemingly unaffected tissue where light tactile stimuli are capable of eliciting itch-like sensations. The term itchy skin or allokinesis has been coined for these secondary sensations that are reminiscent of the features of secondary hyperalgesia evolving around a painful focus. A crucial observation is that itch and pain usually do not co-exist in the same skin region and a mild noxious stimulus

such as scratching is in fact the singly most effective way to abolish itch. This abolition of itch can be prolonged producing an `antipruritic state`. Although mild scratch is often not painful, microneurographic recordings from humans have directly determined that such stimuli are among the most effective ways to excite cutaneous unmyelinated nociceptive afferents. (See, for example: Shelly, W. B. and Arthur, R. P. (1957) Arch. Dermatol. 76, 296-323; Simone, D. A. et al. (1987) Somatosens. Res. 5, 81-92; Graham, D. T., Goodell, H. and Wolff, H. G. (1951) J. Clin. Invest. 30, 37-49; Simone, D. A., Alreja, M. and LaMotte, R. H. (1991) Somatosens, Mot. Res. 8, 271-279; Torebjork, E (1985) Philos. Trans. R. Soc. London Ser. B 308, 227-234; and Valbo, A. B., Hagbarth, K. E., Torebjork, H. E. and Wallin, B. G. (1979) Physiol. Rev. 59, 919-957).

[0004] Physiologically, there is evidence that substance P released from nociceptor terminals can cause the release of histamine from mast cells. Activation of mast cells, with release of the pruritogen histamine, occurs in immediate type hypersensitivity diseases, such as anaphylactic reactions and urticaria. Urticarial eruptions are distinctly pruritic and can involve any portion of the body, and have a

variety of causes beyond hypersensitivity, including physical stimuli such as cold, solar radiation, exercise and mechanical irritation. Other causes of pruritus include: chiggers, the larval form of which secretes substance that creates a red papule that itches intensely; secondary hyperparathyroidism associated with chronic renal failure; cutaneous larva migrans, caused by burrowing larvae of animal hookworms; dermal myiasis, caused by maggots of the horse botfly, which can afflict horseback riders; onchocerciasis ("river blindness") caused by filarial nematodes; pediculosis, caused by lice infestations; enterobiasis (pinworm) infestations, which afflict about 40 million Americans, particularly school children; schistosome dermatitis (swimmer's itch); psoriasis; poison ivy and asteatotic eczema ("winter itch"). The role of histamine or other endogenous pruritogens in mediating itch associated with these and other pruritic conditions, such as atopic dermatitis, is not yet well established. For atopic dermatitis, in particular, it appears that itch is not inhibited by antihistamines, but by cyclosporin A, a drug which inhibits the production of cytokines which have been proposed as potential pruritogens.

[0005] Current therapies for the treatment of itch include a vari-

ety of topical and systemic agents, such as steroids, antihistamines, and some psychotherapeutic tricyclic compounds, such as doxepin hydrochloride. The limitations of these agents are well known to medical practitioners, and are summarized in the "Warnings" and "Precautions" sections for the individual agents listed in PDR Generics. In particular, the lack of complete efficacy of antihistamines is well known, but antihistamines are frequently used in dermatology to treat pruritus due to urticaria, atopic dermatitis, contact dermatitis, psoriasis, and a variety of other conditions. Although sedation has been a frequent side effect of conventional systemically administered antihistamines, a new generation of antihistamines has been developed that are nonsedating, apparently due to their inability to cross the blood-brain barrier.

[0006] Scratch reaction itch, anal itch, irritant itch are due to plants (e.g., poison ivy), insect bite, sunburn, chemical itch, eczema, pruritis dermatitis, diabetic skin itch, aging skin itch, foot-itch, chickenpox, jock itch, hives, itch of healing burns and wounds, dry winter skin itch, and stress-related scalp itch, etc.

[0007] Atopic dermatitis is a skin inflammation that usually develops in early childhood and continues into the teen

years. While few adults who had it during childhood still have severe itch and rash, many continue to have milder symptoms and "sensitive" skin problems. Antihistamines reduce itching by blocking chemical (histamine) processes in an allergic reaction. For many years, antihistamines have been used to reduce the itch caused by atopic dermatitis. Sedating antihistamines have been favored for treating children who cannot sleep because of severe itch at night. However, recent research suggests that atopic dermatitis itch is not caused by histamines. (Kristal L, Klein P (2000). Atopic dermatitis in infants and children. *Pediatric Clinics of North America*, 47(4): 877-895; Klein P, Clark R (1999). An evidence-based review of the efficacy of antihistamines in relieving pruritus in atopic dermatitis. *Archives of Dermatology*, 135: 1522-1525.).

[0008] Pruritus is the medical word for itch. It is defined as a sensation that provokes the desire to scratch. Itching can be a significant source of frustration and discomfort for patients. When severe, it can lead to loss of sleep, anxiety, and depression. The exact cause of an itch is unknown and is a complex process. Ultimately it involves nerves in the skin responding to certain chemicals such as histamine, and then processing these signals in the brain.

Pruritus can be a symptom of certain skin diseases, and sometimes a manifestation of an internal process. In other patients where there is no evidence of skin or internal disease, pruritus may be due to faulty processing of the itch sensation within the nervous system.

[0009] There are many skin diseases that may have itching associated with a rash as a prominent symptom. Examples would be hives, chicken pox, and eczema. Some skin conditions only have symptoms of pruritus without having an apparent rash. Dry skin, for example, is very common in the elderly, and can really itch (especially in the winter), with no visual signs of a rash. Pruritus is usually secondary to subtle dry skin, but it may be a manifestation of an internal condition. Some parasitic infestations of the skin, such as scabies and lice, may be very itchy. Often the dermatologist will be able to diagnose these conditions by examining the skin. When pigmented moles itch, a dermatological opinion should be sought to exclude a malignant change in the mole. Sometimes, however, a skin scraping or a biopsy may be needed to help make the diagnosis.

[0010] There are several internal diseases that may cause itch. The most common example is kidney failure. Other types

of internal diseases that may cause pruritus are some types of liver disease including hepatitis C, and thyroid disease including both hyper (too much) and hypo (too little) thyroid hormone levels. Some blood disorders such as iron deficiency anemia, polycythemia vera, and multiple myeloma can cause itch. Occasionally, lymphomas may have pruritus as a component. Neurologic conditions such as pinched nerves and strokes also may lead to itch.

[0011] The treatment of itch depends on its cause. If the itch is from a skin disease such as hives or eczema, treatment of the skin disease itself generally relieves the itch. If the itch is from an internal disease, patients may require medication to be taken orally, or occasionally may receive ultraviolet light treatments to relieve the itch. Although there are many causes for pruritus, there are some basics which apply to most treatments, for example, avoiding hot bathing or showering, wearing light clothing, and a cool work or domestic environment, using mild soaps, applying moisturizing creams or lotions. . Soaps often dry out the skin. Use mild soaps only in odor bearing regions. After bathing, be sure. For itchy conditions where blistering or weeping of the skin is present, such as chicken pox or poison ivy, taking a cool oatmeal bath, or using topical

drying agents such as calamine, may be helpful. Although pruritus is an often disrupting and disabling symptom it generally responds well to treatment.

DETAILED DESCRIPTION

[0012] In this invention, a combination of herbs and other natural substances is described consisting of Cactus (*Opuntia ficus indica*), Feng Jiao (*Apis mellifera ligustica* Spin) (also known as Bee Propolis), β -sitosterol, and Stearic Acid in which each of the ingredients is preferably in an amount in the range of 1.0 to 20% of the final amount of preparation. In this preparation, Soybean concentrates (containing 40% β -sitosterol used.), and Propolis dilution (5:1) is used. In the foregoing assertion, efforts have been made to find a suitable palliative and/or curative agent for the treatment of various types of skin itch.

[0013] Each component of preparation whether used in its raw form or as an extract is standardized according to its marker compound(s) and factored into final calculation of the amount of extract used for the manufacturing of final preparation. For example, if an extract is used which is 1:10 extract (such as the Cactus extract), meaning that 10 G of the component yields 1 G of extract then the required quantity of the extract for a 5% of original compo-

ment will be provided by a quantity of 0.50 G extract in the preparation. In the case of soybean, a standardized 40% extract is used (Catalog # S 5753 Minimum 40% Soybean, Sigma-Aldrich, St. Louis, MO). In this case, a 2% final concentration of β -sitosterol is provided by 5 G of the above 40% Soybean. In the case of propolis, a 5:1 dilution in ethanol provides a 1% or original propolis by adding 5 G of the diluted propolis. Note that whereas in the case of extracts the yield is more concentrated but in the case of propolis it is a diluted form.

[0014] The extracts and dilutions corresponding to about 1–15%, are mixed together in a stainless steel tank with vacuum and heating implementation and then an amount of vegetable oil, preferably canola oil, is mixed for 10 minutes. Vacuum is then applied while heating the preparation to 40 C to remove alcohol (such as from propolis dilution and Cactus extract), leaving a residue of alcohol not more than one percent in the final preparation. This, however, is not a critical step. The oil mixture is then filtered through muslin cloth to remove any suspended particles. Further the while the preparation is still warm, pharmaceutical grade beeswax in the amount equivalent to final preparation composition of 8%, ranging from 5–12%, is added and

the mixture stirred gently for about 5 minutes at elevated temperature and then allowed to cool in appropriate containers such as laminated plastic tubes or laminated aluminum tubes or jars (laminated plastic, laminated metal or glass). The quantity of wax added is also not critical and can be adjusted to provide a consistency of ointment suitable for topical administration. Different amounts of wax can be added to produce preparations that may be useful for different purposes.

[0015] As is described in Propolis in Natural Therapeutics (1983), 2nd revised edition, published by Librairie Maloine S. A. Editeur, Paris, France, Fragrance Journal, No. 83, pp. 20–28 and pp. 36–43 (1987), and Apidologie, Vol. 22, pp. 155–162 (1991), propolis is a resin-like product, stored by bees in beehives, containing resins, beeswaxes, essential oils, pollens and flavonoids and having been used in a variety of folk medicines for a long time. It has been known that the main activities of propolis are antiseptic activity, antioxidation activity, anti-inflammatory activity, local anesthesia, virus growth-inhibitory activity, immunoregulatory activity, and macrophage activating activity, and that the main ingredients of propolis are flavonoids, aromatic carboxylic acids, and aromatic alde-

hydes. Honey bees collect the sap or resin from trees, such as poplar or birch, combine it with their own enzymes, and create propolis. Raw propolis is composed of 50–70% resins and balsams, 30–50% wax, 5–10% pollen and 10% essential oils. It contains Vitamin B1, 0.20 mg/100 g; vitamin B2 0.60mg/100 g, vitamin B6 0.16 mg/g, vitamin E 3.80 mg/100g, folic acid 7 mg/100 g, pantothenic acid 0.08 mg/100 g, inositol 6 mg/100g. It is rich in trace minerals. And in its raw state, has 500 times more bioflavonoids than oranges. Propolis acts as a natural antibiotic, creating one of the most sterile environments in the animal kingdom. has shown it offers antiseptic, antibiotic, antibacterial, antifungal, and even antiviral properties. Propolis is manufactured by collecting from the frames and boxes of the beehives and collectors place in the hives. Propolis is macerated and dissolved in pure ethyl alcohol and the mixture agitated and matured until a proportion of 20% dilution is achieved. (See: Ceschel GC, Maffei P, Sforzini A, Lombardi Borgia S, Yasin A, Ronchi C. In vitro permeation through porcine buccal mucosa of caffeic acid phenethyl ester (CAPE) from a topical mucoadhesive gel containing propolis. *Fitoterapia*. 2002 Nov;73 Suppl 1:S44–52. ; Kiderman A, Torten R, Furst AL, Reinus

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[0016] Opuntia comprises mainly the whole plant of *Opuntia ficus indica* (Cactacea family) as the main constituents. Other species and varieties of *Opuntia* genus of the Cactaceae family are included here by reference. The reported pharmacologic properties of *Opuntia* include: analgesia, antiinflammatory, antiulcerogenic, antioxidative, affecting activity of aromatase and reductase, free radical scavenger, antiviral, lowering LDL cholesterol levels, glucose-6-phosphatase and fructose-1,6-diphosphatase activity, antidiabetic, a rich source of biologically active alkaloids and other nutritional elements often considered essential for tissue growth. *Opuntia ficus-indica* (Mission Cactus, Yellow Tuna, Prickly Pear, Indian Fig, Nopal) comprises mainly the whole plant of *Opuntia ficus indica* (Cactacea family) as the main constituents. It is indigenous to the Americas as well as South Asia, Southeast Asia and the

Middle East. Other species and varieties of *Optunia* genus of the Cactaceae family are included here by reference. The reported pharmacologic properties of *Optunia* include: analgesia, antiinflammatory, antiulcerogenic, antioxidative, affecting activity of aromatase and reductase, free radical scavenger, antiviral, lowering LDL cholesterol levels, glucose-6-phosphatase and fructose-1, 6-diphosphatase activity, antidiabetic, a rich source of biologically active alkaloids and other nutritional elements often considered essential for tissue growth. It is also an excellent source of beta-sitosterol. I contains mescaline, tyramine, N-methyltyramine. (See: Park E, Kahng J, Lee SH, Shin K. An anti-inflammatory principle from cactus. *Fitoterapia* 2001 Mar; 72(3):288-90., College of Pharmacy, Sookmyung Women's University, 140-742, Seoul, South Korea; Bwititi P, Musabayane CT, and Nhachi CF: Effects of *Opuntia megacantha* on blood glucose and kidney function in streptozotocin diabetic rats. *J Ethnopharmacol* 2000 Mar; 69 (3): 247-52; Gurrieri S, Miceli L, Lanza CM, Tomaselli F, Bonomo RP, Rizzarelli E: Chemical characterization of sicilian prickly pear (*Opuntia ficus indica*) and perspectives for the storage of its juice. *J Agric Food Chem* 2000 Nov 20; 48 (11): 5424-5431; Mtambo MM,

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N. Kozumi, et al., Chem. Pharm. Bull., 27:38, 1979. The source of β -sitosterol however is not relevant. It could be obtained from natural sources or from synthetic sources. β -sitosterol (C₂₉ H₅₀ O, molecular weight 414.72) is a common sterol in plants. It is generally isolated from wheat germ, soybean or corn oil. Sterols are important cyclized triterpenoids that perform many critical functions in cells. Phytosterols such as campesterol, stigmasterol and β -sitosterol in plants, ergosterol in fungi and cholesterol in animals are each primary components of the cellular and sub-cellular membranes in their respective cell types. The dietary source of phytosterols in humans comes from vegetables and plant oils. The estimated daily phytosterol content in the conventional western-type diet is approximately 250 mg in contrast to a vegetable diet, which would provide double that amount. Although having no nutritional value to humans, phytosterols have recently received a great deal of attention due to their possible anti-cancer properties and their ability to decrease cholesterol levels when fed to a number of mammalian species, including humans. Phytosterols aid in limiting cholesterol absorption, enhance biliary cholesterol excretion and shift cholesterol from atherosclerotic plaque.

While many of the mechanisms of action remain unknown, the relationship between cholesterol and phytosterols is apparent. This is perhaps not surprising given that chemically, phytosterols closely resemble cholesterol in structure. The major phytosterols are β -sitosterol, campesterol and stigmasterol. Others include stigmastanol (β -sitostanol), sitostanol, desmosterol, chalinasterol, poriferasterol, clionasterol and brassicasterol. (Gould R. G., Jones R. J., LeRoy G. V., Wissler R. W., Taylor C. B.; Absorbability of β -sitosterol in humans; *Metabolism*, (August) 1969; 18(8): 652–662. Tabata T., Tanaka M., Lio T.; Hypocholesterolemic activity of phytosterol. II; *Yakugaku Zasshi*, 1980; 100(5): 546–552. Hepistall R. H., Porter K. A.; The effect of β -sitosterol on cholesterol-induced atheroma in rabbits with high blood pressure; *Br. J. Experimental Pathology*, 1957; 38: 49–54.). The role of phytosterols, particularly, β -sitosterol in stimulating human stem cells and particularly promoting hair growth has not been reported yet. Several novel applications of phytosterols including β -sitosterol have been reported. The U.S. Patent 5,965,449 to Novak describes a method of assessing risk for cardiovascular disease and other disorders and phytosterol-based compositions useful in preventing

and treating cardiovascular disease and other disorders. The level of serum campesterol and β -sitosterol are determined and their ratio is correlated with the risk of cardiovascular or a related disorder. The U.S. Patent 5,523,087 to Shlyankevich is for a pharmaceutical composition for the treatment of diabetic male sexual dysfunction; it contains physosterogens, phosphatidyl choline, β -sitosterol, Damiana leaf extract and vitamins and minerals. The U.S. Patent 5,486,510 to Bouic, et al., is for a mixture of β -sitosterol glucoside and β -sitosterol is administered to persons for the modulation or control of immune responses. The U.S. Patent 5,747,464 to See is for a composition for inhibiting absorption of fat and cholesterol from the gut and a method for making and using the composition. The composition comprises β -sitosterol bound irreversibly to pectin to form a β -sitosterol and pectin complex. The U.S. Patent 5,118,671 to Bombardelli, et al., is for complexes formed between aescin, cholesterol or β -sitosterol and phospholipids and a method for producing an anti-inflammatory effect is also described.

[0017] Olive Oil is a complex compound made of fatty acids, vitamins, volatile components, water-soluble components

and microscopic bits of olive. Primary fatty acids are Oleic and linoleic acid. Oleic acid is monosaturated and makes up 55–85% of olive oil. Linoleic is polyunsaturated and makes up about 9%. Linolenic, which is polyunsaturated, makes up 0–1.5%. Vitamins are Vitamin E and carotene. The levels of these acids (actually bound to glycerol as triglycerides) varies during the different maturation stages of the olive, varies with the variety and the growing conditions. It is generally accepted that cooler areas (e.g., Tuscany) will give oil with higher oleic acid than warmer climates. Most of the research however has been reported as individual studies so that comparisons are like apples and oranges. However there is a major trial underway in all the major Mediterranean Producing countries with some 10 or so varieties. This study will give more definitive information. Regarding the poly-unsaturated fatty acids (PUFAs) there is a wide range acceptable for EVO, however the Linolenic has to be less than 0.9%. There is no problem if the levels are higher e.g., 1.5% regarding the olive oils nutritional value. But the Linolenic acid level is used to establish the authenticity of the olive oil. Seed oils like Canola have higher levels of Linolenic acid. Also the higher the level of unsaturation i.e. more PUFAs leads to a

less stable oil, however this has to be counterbalanced by the levels of antioxidants that protect the oil (these will also vary by similar factors to the fatty acid profile as well as stress e.g., drought. A higher Linolenic than the IOOC may actually be of benefit nutritionally for reasons other than those associated with oleic acid.

[0018] Other constituents: Phenols, free fatty acids, peroxide, triacylglycerols (TAG), diacylglycerols (DAG), and monoacylglycerols (MAG), thiobarbituric acid reactive substances (TBARS), Pheophytin A and many other substances make up olive oil. The flavenoid polyphenols in olive oil are natural anti-oxidants, which have been shown to have a host of beneficial effects from healing sunburn to lowering cholesterol, blood pressure, and risk of coronary disease. There are as many as 5 mg of antioxidant polyphenols in every 10 grams of olive oil. Many other nut and seed oils have no polyphenols. (See also: Essential fatty acid deficiency in renal failure: can supplements really help? J Am Diet Assoc. 1997 Oct;97(10 Suppl 2):S150-3; Peck LW, Monsen ER, Ahmad S. Effect of three sources of long-chain fatty acids on the plasma fatty acid profile, plasma prostaglandin E2 concentrations, and pruritus symptoms in hemodialysis patients. Am J Clin Nutr. 1996

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[0019] Natural beeswax contains many still yet unidentified components that have for centuries provided healing properties for many ailments. Propolis is just one such example. The isolation of D-002 series of alcohols provides the clue to its anti-inflammatory activity; flavolins and other minor components provide impart many pharmacologic properties to beeswax. (See: Carbajal D, Molina V, Valdes S, Arruzazabala ML, Mas R, Magraner J: Anti-inflammatory activity of D-002: an active product isolated from beeswax. *Prostaglandins Leukot Essent Fatty Acids* 1998 Oct; 59 (4): 235–8.; Tsigouri A, Menkissoglu-Spiroudi U, Thrasyvoulou AT, Diamantidis GC: Determination of fluvalinate residues in beeswax by gas chromatography with electron-capture detection. *J AOAC Int* 2000 Sep–Oct;83(5):1225–8; Carbajal D, Molina V, Noa M, Valdes S, Arruzazabala ML, Aguilar

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rats and rabbits. J Appl Toxicol 1998 Sep-Oct; 18 (5): 313-6; Carbajal D, Molina V, Valdes S, Arruzazabala L, Mas R: Anti-ulcer activity of higher primary alcohols of beeswax. J Pharm Pharmacol 1995 Sep; 47 (9): 731-3; Carbajal D, Molina V, Valdes S, Arruzazabala ML, Mas R, Magraner J: Anti-inflammatory activity of D-002: an active product isolated from beeswax. Prostaglandins Leukot Essent Fatty Acids 1998 Oct;59(4):235-8.; Noa M, Mas R: Effect of D-002 on the pre-ulcerative phase of carageenan-induced colonic ulceration in the guinea pig. J Pharm Pharmacol 1998 May;50(5):549-53.; Rodriguez MD, Gamez R, Sanchez M, Garcia H: Developmental toxicity of D-002 (a mixture of aliphatic primary alcohols) in rats and rabbits. J Appl Toxicol 1998 Sep-Oct;18(5):313-6; Liu F, Sun D: Active constituents lowering blood-lipid in beeswax. Zhongguo Zhong Yao Za Zhi 1996 Sep;21(9):553-4, 576; Carbajal D, Molina V, Valdes S, Arruzazabala L, Rodeiro I, Mas R, Magraner J: Possible cytoprotective mechanism in rats of D-002, an anti-ulcerogenic product isolated from beeswax. J Pharm Pharmacol 1996 Aug;48(8):858-60.; Dorset DL: The crystal structure of waxes. Acta Crystallogr B 1995 Dec 1;51 (Pt 6):1021-8; Carbajal D, Molina V, Valdes S, Arruzazabala L,

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[0020] [Composition of a preferred embodiment]

| Ingredient | Percentage |
|--------------|------------|
| Propolis | 1 |
| Opuntia | 5 |
| β-sitosterol | 2 |

| | |
|--------------|--------|
| Stearic Acid | 3 |
| Olive Oil | to 100 |
| Alcohol | qs |

The preparation described above was applied to itching surface in different situations, chemical itch, wound-healing itch, anal itch, vaginal itch, irritant itch, nervous itch and in all instances an immediate relief was observed. It will be appreciated by those skilled in this art that the above approximate weight percentages are dependent on generally expected potencies of the components, whereby the relative weight percentages will vary sometimes substantially from the above individual amounts. It will be within the skilled person's knowledge with this disclosure that the objects of the present invention require the inclusion of each of the components in relative approximate weight percentages above.